

REMARKS

**1. Claim Amendments**

Method of Making a Kit or Immunogenic Agent Claims

Claims 318 and 322 were inadvertently presented without a transitional phrase between the preamble and the body; this has been corrected. In claims 318 and 322, old step (a) (providing an immunogen is now part of new step (b), and old step (b) is now step (a). Thus, the "comparing" step is the first step. (Within this comparing step, clause (2) has been deleted, and conforming amendments made to the rest of the claim.) Then, in step (b), one or more immunogens is selected for inclusion in the kit, and provided. The remaining steps are unchanged.

In the "comparing" step, reference to markers of CIMD is deleted as superfluous. Also, reference to "severity" has been removed.

New dependent claims 326-336 have basis as follows:

325: Page 19, line 5.

326: Page 36, lines 1-10.

327: Page 35, lines 20-26, but with BCG omitted (note that original claim 1 recited "optionally including at least one immunogen other than BCG.")

328: Ditto.

329: Page 59, lines 12-13.

330: page 32.

331: page 15, lines 4-5.

332: Page 69, lines 24-27.

333: Original claim 18.

334: Page 18, line 19.

335: For different protective antigens for protection against the same infectious agent in general see page 77 lines 17-20, and page 34, line 27 through page 35, line 19; and more particularly note e.g. the comparison of whole cell

and acellular pertussis immunogens, or of Hemophilus influenza polysaccharide and conjugate immunogens. Also note the distinction between screening an immunogen per se for modulation of a CIMD (page 54, lines 4-7; page 55 line 19 et seq.) and screening of an immunization schedule (page 54, lines page 61, line 12 et seq.); and the concept of a strong vs. weak immunogen (page 34, lines 18-26; page 59, lines 14-20; page 70, line 24).

336: page 54, lines 10-13.

337-38: page 21, lines 9-10.

339-41: page 64, lines 27-29.

#### Kit Claims:

Kit claim 59 has been partially reverted back to the form it had as of the Nov. 6, 2006 amendment. That is, the newly added body limitations have been deleted, and the prior labeling limitations reinstated, albeit with certain revisions. Notably, the former clause (b) is omitted and clause (c) is re-designated as (b) and now recites "regarding data from any clinical trial of the effective of said immunogens when administered according to a specific immunization schedule...."<sup>1</sup> Also, clause (b) does not refer to the time of onset and clause (a) does not refer to severity.

For basis for labeling limitations, see page 7, lines 11-14, and the discussion at pages 24-26 of the Appeal Brief filed Aug. 8, 2003.

## 2. Formal Matters

2.1. In response to the objection to the title as not descriptive (OA §4), contrary to the examiner's assertion, methods are claimed. It is respectfully suggested that the

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<sup>1</sup> The old language was "regarding any animal study or clinical study of the effect of any of said immunogens, or of any immunization schedule for any of said immunogens...."

title be amended once there is agreement as to allowable subject matter. Otherwise, the title may need to be revised repeatedly. Consequently, we request that this objection be held in abeyance until patentable subject matter is indicated, pursuant to 37 CFR 1.111(b).

2.2. The status of USSN 08/104,529 has been updated.

2.3. In response to OA §6 trademarks, the objection lacks particularity, and it fails to identify the location of any putative trademarks. In an application which has been pending since 1994 (international filing date), we think the PTO could make more of an effort to be specific about its concerns, having failed to raise the issue during 15 years of prosecution.

We have nonetheless reviewed the specification and addressed the trademarks found at P82, L20, and P86, L7, 11 and 15. We request that any further trademark-related objections be held in abeyance until patentable subject matter is indicated, pursuant to 37 CFR 1.111(b)

### **3. Definiteness Issues (OA §7)**

3.1. In section 7, third paragraph, the examiner "string cites" various clauses of the claim, but does not explain why each of these terms is indefinite.

The terms "incidence", "prevalence", "frequency" and "severity" are routinely used in the epidemiological art and hence do not reasonably raise an indefiniteness issue.

The separate recitation of "risk" has been deleted from the claim.

The term "chronic immune mediated disorder" is defined at page 21, lines 2-12, with examples given on pp. 21-24.

For markers of CIMDs see page 32, lines 23-31. In any event, the term markers is no longer explicitly recited in the claims, although it should be noted that a comparison of incidence of a CIMD might implicitly involve comparison of the level of a marker of that CIMD in the two groups.

The term "immunization schedule" is defined at page 24, lines 23-26, with detailed discussion of schedules at p. 24-27, 29-33 and note also dosages at 46-51, and routes at 52. It thus follows that "according to an immunization schedule" is definite.

The term "associations are statistically significant" does not appear in any of the claims now pending. However, we note that the concept of statistical significance, and methods of determining whether an apparent association is statistically significant, are well established in epidemiological practice.

The term "adequate protection" does not appear in any of the claims now pending. The pending claims do refer to "immunogens being protective, after one or more doses, against at least one infectious disease" (3322)

It implies that there is a statistically significant difference in the incidence rate of the disease, subsequent to immunization, between the treatment group and control group.

A search through Google Patents reveals 3,490 patents/published US applications with the term "protective antigens", 634 for "protective vaccine" and 225 for "protective immunogen". Plainly, the art knows what "protective" means in this context.

The term "substantially reduce the incidence or severity of said chronic immune-mediated disorder" does not appear in the present claims. However, if it were, a standard for judging substantiality is provided by page 32, lines 18-22.

3.2. In section 7, the first four paragraphs on page 4, the examiner suggests that the claims should recite particular immunogens, agents, immunization schedules and methods of determination.

However, the invention relates to the discovery that the choice of immunization schedule against an infectious

disease -- the immunogen per se, or its dosage, or timing of administration, or adjuvants -- can affect the risk of a CIMD.

The purpose of the invention is not to discover vaccines protective against an infectious disease, but rather to make sure that their use is not accompanied by unacceptable risk of a CIMD. Hence, the claim recites testing the risk of CIMD associated with a possible kit as part of the overall process of making the kit.

There is detailed discussion of immunogens at pages 33-36 and 52, and of methods of preparing immunogenic agents at pages 42-44. Methods of identifying "new" immunogens are discussed at pages 54-56. For screening for CIMD, see pages 55-69.

#### 4. Written Description

4.1. The recitations of "at least one different", "each conjugated to at least one", "at least two different acellular", "at least two purified viral capsid" and "to which a human is acceptable", all from claim 59, and to first and second carbohydrate immunogen conjugate with different carrier proteins from 279, no longer appear in the claims. However, we think it reasonable to point out that the examiner never specifically addressed the specific enumeration of basis at pp. 13-14 of the last response.

4.2. With regard to the "comparing" language (rejections §9, 10) original claim 23 recited "comparing the incidence or severity of said chronic immune-mediated disorder or the level of a marker of such a disorder, in the treatment, with that in the control group".

P54, L4-7 teaches screening for whether an agent "modulates at least one chronic immune mediated disorder"; P56, L23, for "inhibiting chronic immune-mediated disorders; P58, L1-4, "for determining if an agent can alter the incidence, prevalence, frequency and or severity of a

chronic immune mediated disorder"; P59, L12-14, for screening vaccines "to determine their propensity to induce... chronic immune mediated disorder"; P59, L25-26, for "determining incidence or prevalence"; P60, L17-20, for screening immunogens "to determine their propensity to modulate at least one chronic immune mediated disorder" or P61, L9, to "modulate the development". The "incidence, prevalence, frequency or severity" mantra reappears at P62, L14-15 and 27-28; P63, L20-21; P66, L5 and 15; P67, L20; P68, L8-9. Reference to "modulation of development" appears again at P62, L23-25. Reference to "a substantial risk of reducing diabetes" appears at P70, L5 and to "the risk of inducing or exacerbating" a CIMD at P70, L15-16 (or "the risk of thereby eliciting" a CIMD at P70, L22-23, or "risks of developing said disorder at P71, L4-5 and 9; P72, L16-17). Page 54, lines 12-13 speak of "preventing or alleviating" a CIMD.

This is ample to meet the "possession" test for written description.

As previously explained, the invention here resides in the recognition that the identity, form and amount of the immunogen, and the timing of its administration, can substantially affect (increase or decrease) the risk of subsequent contraction of a CIMD, or the severity of the CIMD. With that insight, the skilled worker can readily test for the effect of a given immunogen (see points (i) and (ii) at P61, L24-26), dosage (points (iii) and (iv)) or immunization schedule (points (v)-(viii)) on the risk of a given CIMD. There are many known clinical assays for CIMDs.

The rejection acknowledges the analytical approach set forth in the written description guidelines, on pages 12-13, but fails to properly apply it.

For a genus claim, the issue is whether there is written description for a representative number of species. There is WD for a species if it is (1) actually reduced to

practice, (2) complete as evidenced by a reduction to sufficiently detailed drawings or structural chemical formula, or (3) set forth in terms of sufficiently detailed distinguishing identifying characteristics for the complete structure of a product or the acts of a process.

Reviewing the specification, example 1 shows comparing the effects of anthrax and plague vaccines with a PBS control on the incidence of diabetes in NOD mice.

Example 2 shows comparison of anthrax alone, anthrax + diphtheria + tetanus, anthrax + whole cell pertussis + diphtheria + tetanus, and whole cell pertussis + diphtheria + tetanus (DTP), with a PBS control.

Example 4 shows comparison of the effect of anthrax and DTP vaccines on incidence of diabetes in BB rats.

Example 5 shows comparison of the effect of anthrax + acellular DTP vaccine with PBS control on incidence of SLE in MBL/lpr mice.

Example 101 is an epidemiological comparison of the incidence of diabetes. Table I is intercountry analysis for (1) no pertussis no BCG, (2) pertussis, BCG before 2 months, (3) pertussis, no BCG, (4) pertussis, BCG school age, and (5) pertussis + HIB, BCG. Table II is a temporal analysis specific to Finland see discussion at pages 93-94, which relates age to vaccination protocol.

Particular reference is made to the Hemophilus influenza or meningococci polysaccharide vaccines, (1974), measles, mumps, rubella trivalent vaccine (1982), and Hemophilus influenza conjugate vaccine (1986).

Table III is a temporal analysis of incidence of diabetes in Allegheny County, Pennsylvania, and the changes in immunization schedules over the covered period are explained at pages 95-97. This to refers to the Hemophilus influenza polysaccharide (1985) and conjugate (1982) vaccines. Reference is also made to polio, diphtheria, tetanus, pertussis, measles and rubella vaccines.

Table IV is a temporal analysis of the incidence of diabetes in Danish military recruits, as correlated with the smallpox epidemic of 1962.

There is also discussion of the epidemiological data regarding smallpox vaccinations in the Netherlands, see P97, L8-14.

We respectfully submit that this constitutes written description for at least a dozen species of immunogen, including several instances of different immunogens associated with the same pathogen (and thus the same infectious disease). We also submit that since these species have no structural relationship to each other, that they may be deemed representative of the claimed genus.

The examiner appears to forget that claim 318 is to a method of making a kit whose distinguishing feature is the selection of immunogens on the basis of a screening for effect on the risk of CIMD. Any known immunogen may be subjected to such screening and selection process. It is not necessary to support the claimed method that applicant isolate and characterize any new immunogens.

On pages 9-11, the Examiner cites EURODIAB (2000), Wraith (2003), Hviid (2004), Prince (2005), and Biomarkers Definitions Working Groups (2001). The purpose of these citations appears to be to cast doubt on whether, in the circumstances tested, immunization affected the subsequent development of diabetes.

On this we have four comments:

(1) the discussion of these references appears to go to the utility of screening for the affect of an immunogen on CIMD, which is an enablement/utility issue (see below), not a WD issue;

(2) it is clear from applicant's work that the same immunogen may have a beneficial, neutral, or deleterious effect, depending on the immunization protocol. Hence, it is not surprising that these cited studies can report

different results than Applicants because the protocols differ;

(3) the claims here are not to a new vaccine, but to a method, and a screening method may be adequately described even if most of the subjects screened are negative;

(4) even if the examiner does not believe that immunization in fact can alter the risk of a chronic-immune mediated disorder, that doesn't mean that the claimed screening method is not enabled to detect such alteration if in fact it exists.

4.3. Incorporation by reference. The examiner says that we rely on various incorporations by reference in the September 21, 2009 amendment. As far as we know, we mention McAleer '646 on page 14, and Madore and Adams on pages 24-25. The latter's relevance is emphasized by page 31, lines 9-18 that is, applicant conceived of disclaimed any schedules that inadvertently read on the then claimed immunization method of then claim 1 without intent of reducing the incidence or severity of a CIMD. However, the disclaimer language Applicant used in those method of immunization claims is not part of the present claims, because Madore and Adams did not compare for risk of CIMD.

We cannot find in that amendment any reliance on the incorporation by reference of the specifications of other applications in this patent family. Since this case is a CIP, that would not be necessary, unless we inadvertently omitted a portion of the parent case. (In that event, we can rely on 1.57(a).) All the other cases have the same specification as this case or the parent case (08/104,529). Perhaps the examiner misinterpreted the statement on page 16, first full paragraph of the last amendment:

The comparison steps are based closely on claims in other patents of this patent family. The last clause is

introduced to make it clear that a  
"transformation" occurs.

While the language was based on the claims of the other patents, that was just to indicate that the PTO had previously accepted the language in cases have the same specification or an older version of the specification. We were not relying on the specifications of those patents for disclosure lacking here.

That said, we believe that the incorporation by reference of prior patents or non-patent literature documents in their entirety is proper.

The examiner urges (page 8) that to incorporate by reference, the host document must identify with detailed particularity what specific materials it incorporates and clearly indicate where the material is to be found in the various documents, citing various cases:

Applicant is reminded that to incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where the material is found in the various documents. See Advanced Display Systems, Inc. v. Kent State Univ., 54 USPQ2d 1673 (Fed. Cir. 2000) citing In re Seversky, 177 USPQ 144, 146 (CCPA 1973).

The PTO apparently reads this language as forbidding applicants from incorporating by reference the entirety of a referenced document. However, none of the decisions cited by the PTO were asked to consider that issue, and we respectfully submit that all that the cited cases require is that the statement be clear as to what is incorporated - and

applicant clearly states that it is the entirety of the documents in question.

No cogent reason has been advanced as to why an incorporated document might not be relevant in its entirety and if so why it might not be incorporated by reference in its entirety.

In the earliest of the cases cited, In re Seversky, the CCPA explained that for reasons of economy, amplification or clarification of expression, a patent application may incorporate by reference material that is elsewhere written down, "by means of an incorporating statement clearly identifying the subject matter which is incorporated and where it is found." In that case, applicant alleged that an application, merely by asserting that it was a continuation-in-part of an earlier application, incorporated by reference the latter (presumably in its entirety). But it was not the extent of the alleged incorporation that was questioned, but rather whether there was a clear intent to incorporate, and the CCPA held that it wasn't. It never reached the issue of what must be said about "where it is found" and thus that aspect of the statement is dictum not holding.

The standard as quoted by the PTO was apparently from ADS. In that case, the issue was whether a prior art patent had incorporated by reference certain material that was necessary for it to be considered anticipatory. The Federal Circuit did not rule on this issue directly. Rather, it held that the question of whether and to what extent material is incorporated by reference is a question of law, and the district court erred by consigning it to the jury. Plainly, the "detailed particularity" statement, under these circumstances, was dictum, not holding.

The Cook decision quoted ADS, but again there was no question as to "particularity" within the incorporated document. The incorporation-by-reference language at issue referred to "the procedure for preparing intestinal mucosa

detailed in US Patent No. 4,902,508, the disclosure of which is expressly incorporated herein by reference." Thus, the incorporation by reference was limited explicitly to the disclosure of a particular procedure, and all that was needed was to determine the contents of that disclosure.

Zenon cites Cook, but in Zenon the incorporation language was also limited. It said, "Further details relating to the construction and deployment of a most preferred skein are to be found in the patent U.S. Pat. No. 5,639,373, and in Ser. No. 08/690,045, *the relevant disclosures of each of which are included by reference thereto as if fully set forth herein.*"

(emphasis in court opinion). Zenon argued, and the trial court agreed, that this language incorporated "the entire disclosures...." The Federal Circuit disagreed - **not** because it thought that such an incorporation would violate the "detailed particularity" requirement, but because the incorporation was explicitly only of the "relevant disclosures" and implicitly only of those disclosure related to the construction and deployment of a vertical skein. It therefore inquired into what passages of the referenced patents were so incorporated.

The examiner elsewhere cites In re Fouche (1971). In that case, the application recited "prepared as described in Example I of our application no. \_\_\_\_" (the blank appearing in the specification as filed). The CCPA held that this identification was reasonably precise, as it had to be an earlier or concurrently filed U.S. application by the same applicant, with an appropriate Example I, and only one such application had been shown to be on file.

We have examined other cases on incorporation-by-reference, and they are consistent with our position that incorporation by reference of the entirety of a document is acceptable.

In In re Ziegler, 150 USPQ 619 (CCPA 1966) the application relied on another application ("412") for support for certain applications. In the application in suit, the "412" application was discussed, and then the specification continued, "it has now been found that *in the processes set forth....*" (Emphasis in opinion). Ziegler contended that the italicized language was a clear reference to the 412 and two other applications that had been discussed, and thus incorporated them by reference.

The examiner urged, "a mere reference to the copending application without any statement as to what it is relied on for is not sufficient to incorporate the teachings...." The court added, "The examiner would have the reference in the appealed application state a particular example for completion of the disclosure."

The CCPA noted that the instant application related to "an improvement in prior processes", and found that "the subject catalysts disclosed as part of the processes of the three applications are also the subject of the improvements here." Consequently, it held that the teachings of the 412 application were incorporated by reference, even though the instant application had not identified a particular example.

In In re Lund, 153 USPQ 625, 631 (CCPA 1967) stated that the purpose of "incorporation by reference" is "to make one *document* become a part of another document by referring to the form [sic, former] in the latter in such a manner that it is apparent that the cited *document* is part of the referencing document as if it were *fully set forth* therein." (Emphasis added). Note that this standard refers to the document, not merely to an identified portion of a document. However, the court held - as did Seversky - that merely stating that the instant application is a CIP of an earlier application is insufficient to evidence an intent to incorporate it by reference. It is interesting to note that the Lund court commented that the Heritage decision "did not

intend to imply that any manner of reference to an earlier application was sufficient to incorporate the **entire disclosure** or any part thereof by reference into the patent." (italics in original, boldface added).

Plainly, the Lund court considered that with a proper "manner of reference", e.g. saying "is incorporated by reference herein", the entire disclosure of another document could indeed be incorporated.

According to a search on the USPTO database, some 1,150,860 US patents issued since 1976 contain the text "incorporated by reference". Of these, 261,126 recite "incorporated by reference in its entirety" (note that "by", "in" and "its" are "stop words" that are ignored by the search engine, so this also captures "... their entirety". The same is true if the word "herein" is included in the search query.) 31,998 patents recited "incorporated by reference in their entireties." There may be more patents that express the same thought, but in different words. Indeed, 129 patents recite "complete contents of which are incorporated by reference". There thus appears to be a strong consensus in the patent community that a US patent application may properly incorporate by reference another document in its entirety.

37 CFR 1.57(a) specifically allows incorporation by reference of the entirety of a benefit or priority application, without any express incorporation by reference language (and overrules the Seversky-Lund holding that merely asserting that an application is a continuation-in-part of another application is insufficient to incorporate the latter by reference).

37 CFR 1.57(b) allows incorporation by reference of other documents, provided that "a clear intent to incorporate" is expressed in the specification, and (2) the referenced document is clearly identified. The rule does not in fact require identification of the particular portion

of the document relied on, and rule 1.57 was last amended September 10, 2007, subsequent to at least three of the four cases cited by the PTO.

## 5. Enablement Issues (OA §11)

All claims are rejected on the ground that the specification allegedly fails to enable the skilled worker to make and/or use the invention as claimed.

5.1. Under subhead (A), the examiner begins by asserting -- without any literature citation -- that "In vitro and animal model studies have not correlated well with 'methods of comparing the incidence...' and/or 'methods of comparing the risk...' as currently recited...."

Applicant's animal studies were in NOD mice and BB rats, which are well established animal models of diabetes, and in MRL/MpJ-lpr mice, which is a well established animal model of SLE.

The issue of extrapolation from animals to humans was further discussed on pages 70-79 of the August 8, 2003 Appeal Brief.

5.2. On page 15, the Examiner asserts that there is insufficient disclosure of "methods of comparing the incidence... [or] the risk..." of a CIMD.

In order to diagnose a CIMD, one or more diagnostic tests for the CIMD must exist. If so, then it is possible to use that test to determine the incidence of a CIMD in a particular group, and to compare the incidence in different groups. Every study of risk factors for CIMDs makes such a comparison. What was novel and nonobvious here was the recognition that immunization schedules were risk factors.

5.3. In paragraph 3 on page 15, the examiner enumerates various reasons why it can be dangerous to extrapolate from in vitro to in vivo. Since applicant's data is in vivo, this is irrelevant.

5.4. In paragraph 4, the examiner asserts "Here, it appears that the claims recite a description of a problem(s) to be solved while claiming all solutions to it". Many vaccine kits have been made without practicing the applicant's comparing step, so Applicant is not claiming all ways of making a vaccine kit.

5.5. The discussion (pp. 15-16) of "diagnostic specificity and sensitivity and positive and negative predictive value" is moot as applicant is not claiming a diagnostic tool. Particular markers of a CIMD may have greater or lesser predictive value but as long as a CIMD can be diagnosed the "comparing" step may be practiced.

5.6. At pages 16-22, the examiner questions whether the timing of vaccination in fact can affect the risk of subsequent CIMD. As we noted in the Appeal Brief of August 8, 2003, pp. 33-35, this is raising an enablement/utility issue and the proper standard is "credibility". The examiner relies on the previously cited DeStefano and EURODIAB, and Hviid, and newly cites Wraith and Prince (OA pp. 15-19). The examiner concedes that there is also evidence in applicant's favor, but implicitly resolves the conflict of evidence against applicant (OA p. 24). But that violates the credibility standard.

Besides doubting the asserted correlation between immunization and CIMD, the examiner asserts that even if a correlation exists, it's for particular immunization schedules in murine models (p. 20) and perhaps also "ecological" (epidemiological) studies (p. 16), and the claims are not e.g. commensurate with the data (i.e., limited to the immunogens/schedules/subjects of those studies (see OA p. 25).

5.6.1. The examiner does not discuss in detail the evidence in applicant's specification, although the examiner did discount animal studies in general, and epidemiological

studies as support for claims not limited to the specific immunogens and schedules studied, as discussed infra.

The evidence is discussed in detail on pp. 31-32 of the August 8, 2003 Appeal Brief. For the relevancy of the epidemiological data, see page 36 of the 2003 Appeal Brief. Note also the discussion on pages 37-41 of that Appeal Brief of the design of those epidemiological studies.

5.6.2. With regard to the alleged post-filing evidence of non-enablement, the DeStefano and EURODIAB references were discussed in the August 8, 2003 Appeal Brief, with DeStefano on page 60, and EURODIAB on page 59.

The Hviid reference was discussed on page 32 of the September 21, 2009 amendment and in regard to that reference please see the Classen OPMJ article that was enclosed with that amendment.

It does not appear that the examiner has responded to applicant's prior arguments concerning DeStefano, EURODIAB, or Hviid.

Regarding Destefano, Applicant wishes to add that in contrast to what the examiner stated, DeStefano admits (page 3 column 2, paragraph 2) that those who received the hepatitis B vaccine before 14 days of life had half the risk of those who had not been vaccinated. DeStefano admits that his study is not powered to detect moderate changes, even a 50% decrease. DeStefano admits (Page 4, column 2, paragraph 3) again that his study was flawed and can not address whether the hemophilus vaccine causes diabetes.

The DeStefano 2001 article in Pediatrics describes a study that was flawed because it was under powered (i.e. did not contain enough subjects) and was thus unable to detect statistical differences that the present inventor showed in many of his papers as well as in the patent application. Please see table 2. The Varicella (chickenpox vaccine) was associated with an increased risk of 1.16 or 1.02 depending

on the model. This indicates that the varicella vaccine was associated with an increased risk, but the study was not large enough to reach statistical significance. It does not disprove the inventor's findings. In a like manner both the Hib (hemophilus vaccine) and the MMR vaccine were associated with increased risk in both models. The acellular pertussis vaccine was associated with an increased risk in model 2. Even the whole cell pertussis vaccine, while associated with a decreased risk, crossed over 1 in the confidence intervals (upper limit 1.06 in Model 1).

The DeStefano paper is very dated, over 10 years old. The examiner quotes the DeStefano abstract to the effect that the "predominance of epidemiology evidence do not support an association". However new references do support the association between vaccines and not only diabetes but also many other chronic immune mediated disorders, as discussed below.

In conclusion, the DeStefano 2001 article in Pediatrics did not disprove Classen. While its results generally supported Classen's findings it was under powered to provide definitive support.

Wraith (2003) is merely a review of published work up to August, 2002. It does acknowledge two Classen epidemiological analyses (Wraith references 62 and 63, but note the animal data or other epidemiological analyses in the instant specification (see pp. 38-46 of the Appeal Brief for a more comprehensive summary of Classen findings). The Sanjeevi paper that is discussed below is **not** in Wraith's bibliography.

Prince (2005) is cited as discussing biomarkers for diagnosing and monitoring autoimmune disease. Prince does not discuss biomarkers for diabetes or SLE (the two diseases for which Applicant presented animal data), and indeed only gives specifics for rheumatoid arthritis and multiple sclerosis. For RA, Prince lists three degradation product

markers, two degradation enzyme markers, and four immune activation markers. For MS, Prince describes two degradation product markers, two enzyme markers, and two immune activation markers.

Prince comments, "the utility of most of those markers is limited by their restriction to relatively inaccessible anatomic sites (synovial or cerebrospinal fluid)". That may be true, the enablement standard relates to technical feasibility not commercial desirability. These markers could be used.

In any event, claims 318-322 no longer specifically refers to "markers".

5.6.3. Classen filed various post-filing evidence of enablement on October 18, 2002, but the only one of the cited documents that is explicitly considered by the examiner is the Classen and Classen (2001) paper in Medical Hypotheses. (OA p. 21). The paper is discussed only in the context of what it says about the possible mechanisms by which vaccines may affect the onset of IDDM. The examiner is reminded that it is not necessary, for enablement, that the inventor identify the principle of operation of the invention. Uncertainty as to which of several mechanisms are involved (and indeed more than one may be involved) does not support the inference that the cause-effect relationship doesn't exist at all.

The specification does suggest a mechanism of action, and that mechanism remains plausible, in turn supporting the plausibility of the assertion that immunization can affect the incidence of a CIMD. See discussion in the 2003 Appeal Brief, pp. 80-83.

While quoting the one passage of this paper, the examiner fails to consider the conclusion of the Medical Hypotheses paper: "We believe that lack of full comprehension of the mechanisms of action does not detract

from toxicology data linking vaccines to IDDM, nor does a complete knowledge of the mechanism of action need to be known before studying the potential benefits of new immunization schedules."

In particular, the examiner fails to discuss Sanjeevi. Sanjeevi, et al., Ann. N.Y. Acad. Sci. 958: 293-6 (2002) (submitted to PTO on Oct. 18, 2002) examines the effect of BCG immunization on the incidence of diabetes in Southern India. Sanjeevi Table 1 relates to the frequency of autoantibodies in BCG-vaccinated and nonvaccinated diabetic patients; of 137 diabetics (identified by GAD65 and IA-2 (CA512) autoantibodies), 86 were vaccinated with BCG **immediately after birth**, while the remaining 51 had not received BCG at all. Hence, based on Classen's work, it would be expected that BCG immunization would decrease the risk. This was indeed what Sanjeevi observed. The frequency of these autoantibodies was significantly ( $P < 0.0005$  for GAD65,  $< 0.001$  for ICA512) decreased in BCG-vaccinated diabetics (compared to those not vaccinated with BCG. (36% vs. 67% for GAD65, 19% vs. 43% for ICA512), see Sanjeevi Table 1.

Sanjeevi Table 2 is limited to **type 1** diabetes patients. The frequency of the two antibodies was again significantly ( $P < .001$ ) decreased in the BCG vaccinated subjects (54% vs. 100% for GAD65; 23% vs. 62% for ICA512).

Sanjeevi, who has no association with Classen, concludes that "BCG vaccination has an immunomodulatory role and is associated with decreased autoantibody positivity in south Indian diabetic patients, which is in conformity with the observations from animal models of autoimmune diabetes."

5.6.4. Additionally, there is new post-filing evidence of immunizations modulating CIMD. Note that according to the teachings of the present invention, immunization can have a

favorable (decreased CIMD) or unfavorable (increased CIMD) effect, depending on the choice of immunogen, the amount of the dose, the timing of the dosings, and perhaps the adjuvant. Also, because of the influence of these factors, the existence of a negative study (immunization not correlated with increased or decreased risk of CIMD for a particular immunization protocol) does not disprove that there can be such a modulation of risk with alternative protocols.

Wahlberg, Ann NY Acad Sci (2003) notes that the autoantibodies against tyrosine phosphatase (IA-2A) and glutamic acid decarboxylase (GADA) "have been shown to be good markers for the disease process sometimes leading to autoimmune diabetes" (p. 405). With a 90<sup>th</sup> percentile cutoff for positivity, HIB vaccination had an odds ratio of 5.9 (CI 1.4-24.4) (p=0.01) for induction of IA-2A and of 3.4 (CI 1.1-10.8) (p=0.4) for GADA.

Ma, et al., Int. J. Epidemiology (2005) report that Hib vaccination (but not hepatitis B vaccination) is associated with a **reduced** risk of childhood leukemia. (Leukemia is identified as a CIMD at page 21, line 26 of the present specification, as part of the broader category of immune-mediated cancers.)

Hernan, et al., Neurology (2004) conducted a nested case control study on British data for 1993-2000, and discovered that immunization with hepatitis B (but not tetanus or influenza) vaccine was associated with an **increased** risk of multiple sclerosis in the three years following immunization. (for multiple sclerosis as a CIMD, see page 22, line 16 of the present specification).

Gruber, Pediatrics (2005) reports that German data shows that some common childhood vaccinations (measles/mumps, pertussis, diphtheria/tetanus) were associated with a transient **reduction** of atopy (a predisposition toward development of allergic

hypersensitivity) whereas others (polio, Haemophilus influenzae) were not. (Atopic dermatitis is identified as a CIMD at page 22, line 1 of the present specification.)

Fisher, Annals of Epidemiology (2000) reports that in the 1994 NHIS dataset, the odds ratio for chronic arthritis was 6.2 (95%CI of 1.08-35.46) times greater among children age 0-5 years who received the hepatitis B vaccine than those that did not. Note that there were only 14 cases of chronic arthritis in the dataset, 12 HB vaccinated and 2 non-HB vaccinated. ("Rheumatoid arthritis" is identified as a CIMD at page 22, line 17.)

Bremner, Arch. Dis. Child. (2005) reported that late immunization with DTP and MMR had a protective effect against hay fever.

DeStefano, PIDJ (2002) (not to be confused with either the "PIDJ" article by Halsey discussed in earlier rounds of prosecution or with the DeStefano 2001 article in Pediatrics relied on by the examiner) reports an immunization effect on the risk of asthma and then attempts to explain it away. Table 3 shows relative risk of developing asthma associated with childhood vaccinations; while a null effect is reported for DTP, OPV and MMR, for Hib the relative risk was 1.18 (1.02-1.36) and for Hepatitis B it was 1.20 (1.13-1.27).

DeStefano then argues that for various subanalyses (see page 503, col. 1), the relative risk was decreased and concluded that "the results of our main analysis are probably biased upward." However, applicant submits that this is simply an attempt by an individual with a known institutional bias to explain away the logical inference from his own data. Dividing a population into subpopulations reduces the power of the test to identify a risk factor as statistically significant and an interested party may keep trying new divisions until the risk is reduced to apparent statistical insignificance.

5.7. On pages 22-23 the examiner questions enablement for protection or for prophylaxis against an infectious disease.

The specification teaches that an immunogen may be used not only to modulate CIMD, but also to immunize against an infectious disease, see paragraph bridging pp. 32-33. Page 25, lines 17-19, as "contributing" to immunization against an infectious disease. Three "standard" immunization schedules are set forth on page 32. Plainly, these are schedules that were developed with the clinical goal of protecting the subjects against the indicated infectious diseases, without regard for their (previously unsuspected) effect on CIMDs. As noted at page 35, there were several immunogens that were routinely administered to children in developed mid-latitude countries less than sixteen weeks old for protection against infectious disease as of 1992. And as indicated on page 36, there were other immunogens then available as vaccines but not routinely so administered. On page 37, it is taught that an "immunogenic agent" preferably "contributes to the desired effect" against an infectious disease. Page 41, line 26 speaks of achieving an "immunogenic effect". Page 47, lines 10-12 describe a pharmaceutically acceptable dose as one whose clinical benefits outweigh the toxicity. Such benefits may, as noted at line 25, include prevention of an infectious disease.

An "immunogenic dose" is defined by page 49, lines 4-5 as that which protects humans against infectious disease; that is, per line 28, it induces a protective immune response. As noted in the sentence bridging pp. 49-50, the immunogenic dose is known for many immunogens from the literature, cp. page 49, lines 7-13.

It is plain that absolute protection from the infectious disease is not contemplated as page 68, line 11 speaks of "adequate protection" and lines 15-21 suggest comparing the "level of protection" with "i) a group that

received no protection/immunization, (ii) a group that receives a recommended immunization schedule, (iii) an rate that is deemed acceptable by professionals in the field as in those affiliated with the Centers for Disease Control, the American Academy of Pediatrics and or the FDA." Page 72, lines 14-29 discuss determining the "degree of protection" against infectious disease in an individual as a result of prior infection or immunization before deciding upon future immunization.

It must be emphasized that the present invention is not directed to finding new vaccines for protection against an infectious diseases, but rather to choosing among different vaccines (or immunization schedules) -- known or demonstrated to be protective against a particular infectious disease -- in order to reduce the immunization-related risk of a subsequent CIMD.

In this context, it is apparent that the reason for reciting protection against an infectious disease is that such is the *raison d'être* for making the kit in the first place. The invention, however, pertains to choice of which of several possible protective immunogens to include in a kit (claim 318), or which of several possible protective immunization schedules to recite in the labeling of a kit (claim 59).

As the PTO is well aware, applicant has been allowed claims in related cases that recite protection against an infectious disease, see e.g. claim 96 of Classen USP 6,638,739. Moreover, the issue has been raised and resolved in this case before. See for example, pp. 17-19 of the Sept. 7, 1999 amendment; section 10 of the Sept. 2, 1999 advisory action withdrew the rejection for "recitation of protection".

Yet the issue returned, somehow, and we respectfully direct the PTO's attention to sections 10.2 and 10.3 of the May 1, 2000 Appeal Brief. When prosecution was reopened on

June 20, 2000, the PTO did not maintain the enablement rejection based on the protection language.

We are therefore puzzled that it is raised anew now, without any discussion of the arguments we made a decade ago. It is very frustrating to have issues raised, dropped, and then raised again as if they were raised de novo, like a phoenix rising from the ashes.

Extremely detailed information concerning the making of various known pediatric immunogens is provided at page 46, lines 1-17, with further elaboration at page 46, line 18 through page 49, line 2. Methods of identifying new immunogens are discussed at page 60, line 1 to page 61, line 6.

The examiner is reminded that according to In re Strahilevitz, 668 F.2d 1229, 212 USPQ 561 (CCPA 1982), a generic claim drawn to an invention in the immunological arts may be enabled even in the absence of a specific example, whereas the instant claims are supported by several specific examples and by additional detailed discussion of alternatives. Likewise, In re Goffe, 542 F.2d 564, 181 USPQ 429, 431 (CCPA 1978) declined to limit applicant to the "specific materials disclosed in the examples" or to "what he has found will work". See also In re Angstadt, 537 F.2d 498, 190 USPQ 214, 218 (CCPA 1976).

## **6. Prior Art Issues**

Claims 59-61, 84, 108, 116, 277-279, 281, 292, 294, 298, 299-301 and 304-324 stand rejected as obvious over Eckhart in view of Madore, Kniskern, Lyson, Do Cuoto and others.

6.1. As examined, kit claim 59 was in product-by-process form. The examiner argues that the cited references teach all the component immunogens of the claim --albeit without explicit analysis of clauses (1)-(4)- and that the process steps (a) and (b) do not alter the nature of the

product and thus are not relevant to the patentability of the product.

We have reverted claim 59 to its prior form of a kit claim with a labeling limitation, so the examiner's comments on product-by-process practice are now moot. We have also excised the "said kit comprising..." and "wherein at least one of the following conditions holds...." limitations, so we needn't consider those further.

6.2. We appreciate that it is still the examiner's position that the labeling limitation (cp. examined claim 306) is not entitled to patentable weight and we previously acknowledged relevant case law, including In re Ngai.

We explained at length (pp. 44-54 of the last amendment) why we believe that for drug, labeling should nonetheless be given patentable weight.

As we commented previously, it does not appear likely that there will be a meeting of minds between the applicant and the examiner on the "functional relationship" issue and we expect that the matter will ultimately need to be resolved by the Federal Circuit, possibly en banc. We retain the claim to preserve our right of appeal.

6.3. We do not believe that the art has been fairly applied to the method-of-making-a-kit claims (318-321). Since these are process claims, every step is entitled to patentable weight, and the PTO has made no showing that any of the references teach the instant "comparing" step as part of vaccine development and manufacture.

Generally speaking, in patent practice, all limitations are entitled to patentable weight (MPEP 2143.03). This is true even if the limitation is deemed indefinite (MPEP 2143.03(I), 2173.06) or lacking in support (MPEP 2143.03(II)).

We respectfully submit that although the "comparing" step does not require a physical action for the invention as claimed to be infringed, that the cited comparison would be

impossible if there were no prior physical action, i.e., examination of the members of the groups to determine whether they exhibited signs of a chronic immune-mediated disorder.

Moreover, even if the "comparing" step was ignored for purposes of determining patent-eligibility under 35 USC 101, it does not follow that it would be ignored for purposes of determining novelty and non-obviousness. That is, since the claim meets the Supreme Court's machine-or-transformation test, the usual rule that all limitations are considered should apply.

## 7. Double Patenting Issues

7.1. All pending claims are rejected for obviousness-type double patenting over all claims of the '385, '139, '739 and '790 patents. It is important to understand the filing relationships among the cases.

The instant application is the U.S. national stage of PCT/US94/08825. PCT '825 was a CIP of 08/104,529, which issued as the '385 patent (Classen=1).

The '283 patent issued on 450,586, a division of PCT '825 and thus of the instant application. (The claims were directed to the invention defined as group III (claim 36) in the office action mailed February 8, 1994 in 08/104,529.) The '139 patent issued on 09/611,415, a continuation of the instant application. The '739 patent issued on a continuation of '415. The '790 patent issued on a continuation of the present application.

The examiner states correctly that 35 USC 121 bars a double patenting rejection only of a divisional application over a parent application (or vice versa). However, for double patenting rejection to be proper, the claims of the instant application must be obvious over the claims of the

reference patent<sup>2</sup>

7.2. According to our records, the February 8, 1994 office action on the parent case (08/104,529) made a three way restriction, as follows:

- (I) claims 1-18, 21-25 and 37 (methods of immunization)
- (II) claims 19-20 (kit and immunogenic agent)
- (III) claim 36 (method of screening at least one potentially pharmaceutically acceptable dose for the ability to modulate the development of CIMD).

Inventions II and III were deemed related as product and method of use, and distinct because the product could be used in a materially different process, such as an assay for circulating antibodies. Inventions III and I were said to have "no features in common".

A provisional telephone election of group I was made, and affirmed by applicant's July 8, 1994 response.

We previously asserted the benefit of 35 USC 121 here against the '283 and '385 patents because there was a restriction in the parent case between kit and method of use claims. The availability of 121 protection against the '385 patent is now in doubt because this case is a CIP and hence does not meet the statutory definition of a divisional application under the reasoning of Pfizer v. Teva Pharms. USA, 86 USPQ2d 1001 (Fed. Cir. 2008).

However, the court overlooked the last sentence of section 121, which implies that a divisional may be a CIP. That sentence reads, "If a divisional application is directed solely to subject matter described and claimed in

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<sup>2</sup> And indeed we believe that in view of the number of times the PTO has reopened prosecution after applicant filed an appeal brief, this is a situation in which two-way obviousness should be required, see MPEP 804(II)(B)(1)(b).

the original application as filed, the Director may dispense with signing and execution by the inventor. The validity of a patent shall not be questioned for failure of the Director to require the application to be restricted to one invention." If a divisional is always directed "solely to subject matter described in the original application," then this sentence is irrelevant and has no meaning, which is not preferred in statutory construction. At the very least, we should be able to enjoy 121 protection for subject matter in a CIP which is directed to the withdrawn invention of the parent case and supported by the disclosure of the parent case.

Consequently, we respectfully submit that 35 USC 121 bars consideration of the '385 patent.

7.3. It is noted that some of the rejected claims are directed to kits, whereas the cited claims of the '385, '739, '139 and '790 patents are directed to therapeutic methods.

Regardless of whether the safe haven of 35 USC 121 shields the instant application against a DP rejection based on the '385, '739, '139 and '790 patents, a holding of obviousness-type double patenting is improper if the inventions, under US restriction practice, are considered patentably distinct. Compare MPEP 802.01(II) with MPEP 804(II) (B) (1), and see also MPEP 806.

This case is the national stage of a PCT application, hence PCT unity rules determined which claims would be examined. While that meant that both kit and method-of-use claims were examined here, it must be remembered that the PCT unity rules relate to examination procedure, and do not override the substantive national law of patentability. Hence, double patenting determinations should still be based on MPEP Chapter 800, even when the application in question is a PCT application. That is to say, the issue of whether the instant claims are distinct from those of the reference

patents is to be adjudicated in accordance with MPEP Chapter 800, without regard to whether the inventions would be considered to have unity under PCT practice.

Under U.S. practice, restriction is proper between (1) product and method of making vs. (2) method of use, assuming the product and method-of-use are distinct. See MPEP 806.05(i).

MPEP 806.05(i) states "applicant may be required to elect either (A) the product and process of making it; or (B) the process of using. Thus, process of making and process of using are deemed distinct.

In the parent case, as previously discussed, we received a restriction between the method-of-use claims and the kit claims, i.e., the examiner held that these were two distinct inventions for purposes of both examination and double patenting.

Even if pursuing the kit claims in a PCT/CIP forecloses reliance on 35 USC 121, the restriction in the parent case operates as a finding by the PTO (that guided prosecution in this case) that the kit and method-of-use inventions are distinct, and this finding is equally relevant for double patenting as for restriction.

In the May 4, 1999 action on this case, section 3, the examiner agreed that in view of the prior restriction between kit and method of use claims, the kit claims should not be rejected for double patenting over the method of use claims of the '283 and '385 patents.

We appreciate that in Pfizer, the Federal Circuit held that the claimed use was not patentably distinct from composition of the reference patent claim. However, the decision did not discuss restriction practice, and the USPTO has not acceded in the decision by amending restriction practice (MPEP 806.05(h) and (i)) to acknowledge that restriction between product and method of use is improper.

The Pfizer decision does not mention restriction

practice, although it cites MPEP 804.01 in the 35 USC 121 context.

We recognize that in In re Russell, 112 USPQ 58, the CCPA stated that 35 USC 121 "is clearly limited to cases in which there has been an actual requirement for restriction" and doesn't apply when the applicant voluntarily files separate applications for restrictable inventions.

However, Russell is inapplicable here because the parent to the instant PCT application did receive an actual requirement for restriction and the instant kit claims are consonant with the unelected kit invention of that case.

But even if applicant is not entitled to the absolute protection of 35 USC 121 on the grounds that the instant application is a CIP, we respectfully submit that there should a presumption against obviousness-type double patenting when the two inventions would have been considered distinct under US practice. In re Coleman, 90 USPQ 10, 104 (CCPA 1953) states "The intermeshing doctrines of division and double patenting are not designed to be a mere trap for the unwary. The two questions are inextricably interwoven and the issues involved in a requirement of division cannot be disregarded where the rejection is on ground of double patenting. If division would have been necessarily required in the first instance, then double patenting cannot be urged if the copending claims issue in separate patents."

Under Federal Circuit procedure, the decisions of its predecessor court, the CCPA, are binding precedent. Moreover, a mere panel of the Federal Circuit does not have power to overrule a prior decision of the Federal Circuit (or thus of the CCPA), that may only be done en banc. Pfizer was not an en banc decision and thus could not overrule Coleman - which indeed it appeared to have overlooked. And if it did overlook Coleman, then there is even less reason to give it deference on the issue.

In Coleman, a claim to a cellulosic wrapping sheet

containing at least 0.3% dehydroacetic acid was held valid over a reference claim to a method protecting foods from microbial attack by wrapping the food in a wrapper containing an effective amount of dehydroacetic acid.

We note that here, none of the claims of the reference patents recite a kit or labeling for a kit or even an immunogen, as required by the instant kit claims.

7.4. With regard to the claims (e.g., 318) drawn to a method of making a kit, this is distinct from a method of using a kit as previously claimed. It is distinct under US restriction practice, which is relevant per Coleman, and it should be evident that it is possible to make a kit without first practicing the comparing step, or a selection of immunogens based on that comparing step, as recited in claim 318.

Method claims have been found to be distinct for purposes of obviousness-type double patenting. For example, in *General Foods Corp. v. Studiengesellschaft Kohle mBH*, 972. F2d. 1272, 23 USPQ2d 1839 (Fed. Cir. 1992), a claim to a process of decaffeinating raw coffee was held to be patentably distinct from a reference claim to a process obtaining caffeine from green coffee, even though the first step of both processes was essentially identical. (It can be argued that the process of decaffeinating was as much a process of making caffeine (the removed byproduct) as of making decaffeinated coffee.)

The 385 claims are directed to a method of immunizing a mammal and do not recite a comparing step at all.

The 139 claims reciting immunizing a mammalian while reducing the risk of said subject thereby developing at least one CIMD which comprises (I) screening a plurality of **immunization schedules** and then immunizing a subject

according to a particular **immunization schedule**. There is no reference to making a kit comprising immunogens, let alone of screening **immunogens** for risk of CIMD as a step in making the kit.

Most of the 739 claims (e.g., claim 1, 71, 96 and 98) are similar to 139 claim 1. 739 claim 104 is a method of protecting a subject which comprises immunizing said subject "where it has previously been determined that the **timing of first immunization** of at least one of said immunogens influences the risk of said subject thereby developing said disorder...." Claim 109 and 110 are business method claims that don't recite the final immunization of the subject but do recite comparison of risk of CIMD and then "determining one or more **methods of immunization** with said immunogens" (109) or "selecting an **immunization schedule**" (110).

The sole independent claim of the 790 patent is drawn to "a method for safely immunizing a human with one or more doses of one or more immunogens which induce protective immunity to one or more infectious diseases when administered according to one or more immunizing schedules." This method has three steps, (I) "considering the association between said immunization schedule and one or more" CIMDs ..., (II) "screening one or more potential recipients and identifying at least one subject who would be expected to be immunizes safely..." and (III) immunizing said human ... by a method identified in (I)". Clause (I) further requires that the effects of **different immunization schedules** be compared. It is thus similar to the 739, except that it is further qualified by the subject screening step.

Generally speaking, the present method of making a kit claims relate to determining which immunogens to include in the kit, whereas the prior method of use claims relate to which subjects to immunize and at what times (the immunization schedule). Hence, we respectfully assert that

they are patentably distinct, and the rejections for double patenting should be withdrawn.

7.5. The Examiner says that the argument based on PTO restriction practice is "is not found persuasive given the long prosecution of both methods and products for eight (8) years".

However, we do not believe that the length of co-prosecution is relevant. If this were a domestic case, then under MPEP 811, the restriction could be made "at any time before final action" -- even after eight years.

Moreover, Applicants received numerous actions in this case that, while rejecting or provisionally rejecting the then pending method-of-use claims over method of use claims in various related Classen patents or applications, accepted the distinctness of the kit claims over those same reference claims. (See Appendix 1.) Indeed, the PTO has treated different methods of use of the kit to be distinct (see e.g., June 18, 2004 restriction).

The reason we could prosecute both product and method claims in the same case is that the PCT permits that, provided that the product avoids the prior art and the method-of-use claims incorporate the product limitations. However, the double patenting doctrine is totally a creation of U.S. law and hence properly references how the case would have been restricted under U.S. practice.

It should perhaps also be noted that this case has gone on for many years because of repeated delays on the part of the PTO -- delays that applicant is not compensated for because this case was filed prior to enactment of the patent term adjustment provisions.

With regard to the DP rejection of method-of-making claims, such were newly added by the last amendment and were never presented in the reference cases. Consequently, the "eight years" argument doesn't seem applicable to them.

7.6. Applicants respectfully assert that the proper standard for obviousness-type double patenting in this case, at least with regard to the later-filed application-based '139, '739 patent and '790 patents, is the two-way obviousness standard, per MPEP 804(II)(B)(1)(b).

While PCT unity practice permitted a single method-of-use to be pursued in the instant application, it could not be expected that the distinctly different methods-of-use patented in the three patents cited could be pursued here. Hence, the patent claims could not reasonably be considered to have been filable in this application.

Secondly, there is a clear showing of administrative delay vis-a-vis the instant application. In the instant prosecution, applicant received his first action on the merits almost three years after filing the application. That is, of course, already longer than the 14 months pendency to first action that is the norm sought for under the later-enacted patent term adjustment provisions.

After two rounds of prosecution, applicant filed his first appeal brief on May 1, 2000, i.e., more than a decade ago. Instead of filing an examiner's examiner, the PTO reopened prosecution. After several more rounds, applicant filed his second appeal brief on Nov. 5, 2002. Questions were raised about applicant's reliance on certain evidence which led eventually to the third appeal brief filed on Aug. 8, 2003. The PTO again reopened prosecution June 18, 2004 - ten months later.

There have been several additional rounds of prosecution since then, with long time lags on the PTO's part. For example, Applicant filed a response on Nov. 3, 2004, and the next action was Dec. 13, 2006 - two years later. Applicant responded to that on March 27, 2007, and the next action was April 20, 2009. And then Applicant responded on September 21, 2009, and the instant office action was mailed Sept. 15, 2011. Thus, three times the PTO

has taken about two years to act on an already old case - which should have been handled on an expedited basis since it was way more than five years old - even though the normal time to act on an amended case is two months and, if this case were under the PTA provisions, there would be compensation for a hiatus of more than four months.

In contrast, the total of all extensions requested by applicant during this prosecution, up until the instant office action, was 14 months. We think it clear that the PTO is "primarily responsible" for the delay in the resolution of this proceeding.

7.7. We request that all of the provisional DP rejections citing copending applications be held in abeyance. Since these are later-filed applications, if the non-DP rejections of this case are overcome, the provisional DP rejections would be withdrawn pursuant to MPEP 804(I)(1). We note that a "provisional rejection" is a rejection by courtesy only; there is no present legal basis to reject, just notice of intent to reject in the future if the reference application issues.

## **8. Procedural Issues**

The enablement evidence derived from third parties is discussed at pp. 46-47 of the November 5, 2002 Appeal Brief. The Examiner deemed the submission of this evidence after final to be untimely, forcing it to be excised from the appeal brief. However, since prosecution was reopened, this evidence should have been considered.

The Examiner nonetheless refused to consider the Declaration (II) of Dr. Bart Classen, with 19 attached exhibits, filed October 8, 2002, and the third IDS with references KA-KC filed December 12, 2002. A Petition for Supervisory Review was filed July 1, 2009.

This petition is now "acknowledged" (pp. 24-25), but

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Applicant's evidence is discussed in only the most generalized way, with the only evidence specifically addressed being Classen, Medical Hypothesis 57:532-8 (2001). The present Examiner does not explicitly acknowledge entry and consideration of Declaration (II) and the 19 exhibits, or of references KA-KC. The PTO has denied Applicant due process by failing to clearly decide the petition and to either grant it and explicitly enter and consider the evidence cited, or deny it and explain why the evidence cannot be entered even though prosecution was reopened.

Respectfully submitted,

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Enclosures

- Wahlberg (2003)
- Ma (2005)
- Gruber (2003)
- Fisher (2000)
- Bremner (2005)
- DeStefano (2002)
- Hernan (2004)
- Appendix I

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Appendix I

The IPER dated 09/03/1995 and prepared by the EPO held that there was a lack of unity between I) the use of the immunogen in the manufacture of a composition or kit, and a kit for use, ...to reduce the incidence or severity of a CIMD, and II) an immunogenic agent comprising a pediatric immunogen and a non-pediatric immunogen according to claim 10.

The October 2, 1998 office action §16 rejected claims 2-17, 19, 21, 23-33 and 34-55 for obviousness type double patenting over claims 1-42 of Classen USP 5,728,385 and 1-47 of USP 5,723,283.

The March 25, 1999 amendment stated in §1.1:

Both method and kit claims are presently pending. Applicant would be willing to cancel the method claims (without prejudice or disclaimer) if the Examiner would allow the "kit" claims.

Also, in section 1.3, Applicant added:

The double patenting rejection is improper as it relates to the "kit" claims, as they were restricted out in the parent case, see 35 USC §121. After all other issues are disposed of, Applicants will either (a) file a terminal disclaimer, or (b) cancel the method claims.

The May 4, 1999 office action maintained the double patenting rejection as to the method of use claims 6, 32 and 33, but not as to the kit claims ("Applicant's argument that the kit claims were restricted out in the parent case is persuasive").

The September 7, 1999 amendment requested that the DP rejection be "held in abeyance until the kit claims (which are free of this rejection) are allowed. At that time, Applicant will either cancel the method claims, or file a terminal disclaimer".

On November 5, 2001, the examiner restricted claims drawn to methods of immunization comprising identifying first and second groups of mammals (153-155, 158-9, 161-258, 260, 261), methods of simultaneous immunization for infectious disease and CIMD (259), and business methods (262-265) from the original (thus, constructively elected) kit and method claims.

In the December 12, 2002 Request for Reconsideration, page 11 note 2, Applicant promised to "immediately cancel the method claims if the Examiner agreed to allow the kit claims".

- On June 18, 2004, the Examiner restricted among
- (I) methods of reducing the severity or incidence of a CIMD, and kits for such
  - (II) methods of protecting against an infectious disease
  - (III) methods of packaging a vaccine,
  - (IV) methods of developing human vaccines.

In the April 20, 2009 office action, the examiner held that the instant method of use claims and those of the '283 patent were distinct. However, for the first time since 1999, the obviousness-type double patenting rejection over '385 patent was at least nominally applied to the kit claims. Also, the '139 and '790 patents were newly cited as reference patents. However, the body of the rejections only asserted that the reference methods anticipated "the instant methods of immunizing", without any specific discussion of the kit.